Remarks

The issues and rejections set forth in the July 16, 2003 Office Action have been reviewed and are summarized herein.

First, the Examiner notes that the restriction requirement is made final. For clarity of the record, applicants wish to note that claims 29-31, 41-43, 48-54, and 58 are not described in the Office Action as considered or withdrawn. Further, claims 30-31 are listed as rejected under 35 U.S.C. §112 second paragraph, and claims 29-31 are listed on the office action summary form as rejected. However, these claims were not part of elected Group I, and accordingly, applicants have treated these claims as withdrawn.

Next, the Examiner rejects claims 1-12, and 19-21 under 35 U.S.C. §112 first paragraph as allegedly lacking written description.

The Examiner then states that claims 1-12, 18-21, 30-32, 34-35, and 37-40 are rejected under 35 U.S.C. §112 second paragraph as allegedly vague and indefinite.

Finally, the Examiner rejects claims 19-21 under 35 U.S.C. §102(e) as allegedly anticipated by Bowen et al., US Patent 6,284,539.

These rejections constitute all of the grounds set forth in the July 16, 2003 Official Action for refusing this application. Applicants respectfully traverse these rejections in view of the present amendments and arguments advanced below.

Claims 1-15, 19-21, 23-43, 48-54, and 58-61 are pending in the application. Claims 1-12, 19-21, and 32-40 are under consideration.

In accordance with the present amendment, claims 1 and 10 now refer to the factor or factors being secreted from a Type 1 astrocyte of the ventral mesencephalon, as is experimentally demonstrated in the application, and explicitly recited at

page 20, lines 28-31.

Claim 32 is amended to substitute "allows binding" for "may result in interaction" in step (a), and to substitute "binding" for "interaction" in step (b). Basis for the amendment can be found for example on page 21, especially lines 26 to 33.

Claim 33 has been amended to depend from claim 32. Dependence on claim 22 is obviously the result of a typing error (see original claims 32-34.) Accordingly, in the listing of claims, claim 33 is listed as "currently amended". Please also note that, claims 33 and 36 (which depends on claim 33) should be re-joined into Group I for Examination.

New claims 59-61 have been added. These new claims correspond to claims 19-21, but are dependent on claim 4.

The Claims Fully Meet the Written Description Requirement of 35 U.S.C. §112 First Paragraph

The rejection of claims 1-12, and 19-21 under 35 U.S.C. §112 first paragraph as allegedly lacking written description cannot be maintained. As noted in the MPEP at § 2163,

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.
>
> Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention.

Furthermore, the written description guidelines set forth in the Federal Register Vol. 66, No. 4, January 5, 2001 states that "An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics, so long as a person skilled in the art would recognize that the inventor had possession of the claimed

invention."(page 1105, column 3). "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, ie: complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics." (Page 1106, column 1).

The Examiner asserts that the claims are not adequately described because the specification does not describe any specific factor, and the claims encompass both secreted and non-secreted factors.

Applicants submit that the claims as amended meet the written description requirement. The inventors have shown that dopaminergic neuronal fate can be induced in a neural stem or neural progenitor cell expressing Nurr1 above basal levels, by contacting the cell with a factor or factors secreted from a Type 1 astrocyte of the ventral mesencephalon, as reflected in the presently amended claims (see for example, page 38 of the specification). Thus the invention as claimed has been reduced to practice.

Accordingly, the claims meet the description requirement, because they have been reduced to practice, and because they show sufficient identifying characteristics of the factors of the invention. Specifically, the claims now recite that the factors are secreted from Type 1 astrocytes of the ventral mesencephalon. At page 38 it is demonstrated that secreted factors from Type 1 astrocyte of the ventral mesencephalon induce dopaminergic neuronal fate in neural stem cells. Thus, the instant specification describes the source of the factors, the means for obtaining the factors, and chemical properties of the factors (that they are secreted and induce a

dopaminergic neuronal fate in a neural stem or neural progenitor cell expressing Nurr1 above basal levels), and shows reduction to practice by inducing a dopaminergic neuronal fate in a neural stem or neural progenitor cell.

Accordingly, applicants respectfully submit that the claimed subject matter is described so as to comply with 35 U.S.C. §112, and request withdrawal of the rejection.

The Claims Fully Meet the Requirements of 35 U.S.C. §112 Second Paragraph

Applicants respectfully take exception to the Examiner's contention that claims 1-12, 18-21, 30-32, 34-35, and 37-40 are vague and indefinite.

First, the Examiner rejects claims 1, 32, and 34 as allegedly indefinite in the recitation "above basal levels", which the Examiner regards as subjective and not clearly defined.

"Expressing Nurr1 above basal levels within the cell" is defined in the specification on page 4 lines 1 to 6, where it is explained that it means expressing Nurr1 at levels greater than that at which it is expressed in the (unmodified) cell *in vivo* under non-pathological conditions.

The expression "above basal levels" is clear to the person skilled in the art. The skilled person understands that the basal level is the level of expression of Nurr1 that is observed in a neural stem or progenitor cell in the absence of modification and under non-pathological conditions. If Nurr1 expression has been increased by modification of a cell, then the expression in that cell is above basal levels.

Expression at a basal level has no significance; it is only when expression is above basal levels that there is any physiological relevance as required in the context of the present invention.

The specification describes (page 4, line 8 onwards) how expression of Nurr1 above basal levels may be achieved by, for example, increasing transcription or translation of endogenous Nurr1 or by introducing one or more extra copies of Nurr1 into the cell. The skilled person therefore knows how to express Nurr1 at above basal levels. By using such a method, it can be ensured that expression is above basal levels. Otherwise, in the absence of pathology, expression will be at basal levels.

The gist of applicants' invention involves expression of Nurr1 above basal levels. It is unnecessary to translate this to a numerical value. The skilled person knows whether expression of Nurr1 is at basal levels and when it is above basal levels, because in practice he knows the conditions in which the cell is placed.

Therefore, in summary, the expression "above basal levels" is clear and readily understood by the skilled person.

The Examiner then rejects claim 1 as allegedly vague and indefinite for the recitation of "obtainable". Applicants respectfully submit that the term "obtainable" is clear, and readily understood by the skilled artisan. Nonetheless, in the interest of expediting prosecution, and without acquiescing to the Examiner's rejection, applicants have amended claim 1 to recite that the factors are "secreted" from a type 1 astrocyte.

Lastly, the Examiner rejects 32, for the allegedly unclear recitations "may", "interaction", and "determining interaction". Again, applicants respectfully submit that the terms as originally recited are clear. Again, in the interest of expediting prosecution, and without acquiescing to the Examiner's rejection, applicants have amended claim 32 to remove the terms objected to by the Examiner.

Accordingly, all of the rejections under 35 U.S.C. §112

second paragraph are believed overcome.

The Claims are Patentable Over Bowen et al., US Patent 6,284,539

The Examiner rejects claims 19-21 under 35 U.S.C. §102(e) as allegedly anticipated by Bowen et al., US Patent 6,284,539.

The Examiner alleges that "There is no evidence of record to indicate that the dopaminergic cells obtained by the methods of Bowen et al would be distinguishable by some structural/functional feature from those claimed herein".

However, it is evident from a comparison between the features of the cells provided and described by Bowen and those of the present invention shows that the two are quite distinct.

Both the properties of the TH+ cells and the preparations of cells produced by the respective methods are different. The method of Bowen gives rise predominantly to non-dopaminergic neurons (96.5% are TH-negative cells), while in a method according to the instant invention the results provide a majority of TH-positive+ cells (e.g. 90%). Bowen states in example 3 (foot of column 11):

> "….only a fraction of the flgNurr1-transduced cells could be induced to express TH and thus the number of flgNurr1-immunoreactive cells in these cultures far exceeded the number of TH+ cells in these cultures. In a typical experiment, only 3.5% of flgNurr1 positive cells were also immunoreactive for TH at 3 d after transfection".

In example 4 he states:

> "pCMVflgNurr1-transfected cultures treated with forskolin had 911.3.±.221.3 cells per mm2 of which 16.1. ±.0.52 or <u>1.77% were TH+</u>" [emphasis added]

This distinction is important because when cell preparations produced according to the Bowen method are transplanted into patients, most of the effects will be related to non-dopaminergic neurons, whereas using the method of applicant's invention most of the effect will be due to dopaminergic neurons, which is indeed what is needed. The goal of the therapy is to replace the population of neurons that is lost by disease (the TH+ dopaminergic neurons), without adding extra unwanted cells that will integrate in the brain and could be deleterious for brain function. The resulting treatments will be in fact essentially different.

The number of TH+ cells that Bowen maximally obtains is comparable only to what the present inventors consider as background levels in their experiments, i.e. the number of TH+ cells obtained when stem cells are differentiated without treatment in accordance with the present invention (see for example Figure 2a in the present application, second column from the left showing about 1% TH+). Such a low number of TH+ cells can be accounted for by an up-regulation in expression of TH, which does not represent an indication of a dopaminergic phenotype.

Moreover, the properties of the TH+ cells in the Bowen method, as disclosed in Example 5 of US 6,284,539, are different from those of the invention. Bowen indicates that the very few TH+/Nurr1+ cells produced by their method do not have neuronal morphology, and do not express the neuronal marker MAP2. See Bowen Example 5 (bridging columns 12 and 13):

> "As is evident in FIG. 2, the morphology of TH+ cells in the flgNurr1-transfected cultures was non-neuronal in contrast to the typical TH+ neuronal morphology seen occasionally in the sham- or control-

transfected cultures. Consistent with their non-neuronal morphology, the TH+ cells in flgNurr1-transfected cultures co-expressed nestin (FIGS. 5A & 5B) and were negative for MAP2, a marker of mature neurons (FIGS. 5C & 5D).

To determine whether these cells expressed cytochemical markers associated with differentiated neurons, we stained transfected cultures with mAb AP-20 which recognizes the a and b isoforms of MAP2 that are expressed by mature neurons. In these experiments, we found that few TH+ cells in the flgNurr1-transfected cultures co-stained for MAP2a/b (FIGS. 5C & 5D)." [emphasis added]

On the other hand, in accordance with the present invention TH0+/Nurr1+ cells show neuronal morphology and express neuronal markers, and are distinguishable on this basis from the TH+ cells described by Bowen.

Accordingly, because the methods of Bowen produce different composition of cells, and cells with different properties than the cells of the instant invention, applicants respectfully submit that the compositions are patentably distinct, and accordingly, the rejection should be withdrawn.

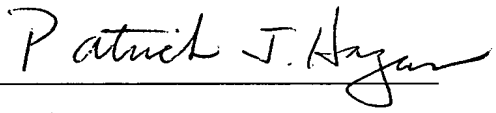
CONCLUSION

In view of the present amendments and foregoing remarks, it is respectfully urged that the rejections set forth in the July 16, 2003 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

DANN DORFMAN HERRELL and
SKILLMAN, P.C.

Attorneys for Applicant

By 

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